Considerations for Antiretroviral Use in Patients with Coinfections

HEPATITIS B (HBV)/HIV COINFECTION (January 10, 2011)

Panel's Recommendations:
- *Prior to intiation of antiretroviral therapy (ART), all patients who test positive for hepatitis B surface antigen (HBsAg) should be tested for hepatitis B virus (HBV) DNA using a quantitative assay to determine the level of HBV replication (AIII).*
- *Because emtricitabine (FTC), lamivudine (3TC), and tenofovir (TDF) have activity against both HIV and HBV, if HBV <u>or</u> HIV treatment is needed, ART should be initiated with the combination of TDF + FTC or TDF + 3TC as the nucleoside reverse transcriptase inhibitor (NRTI) backbone of a fully suppressive antiretroviral (ARV) regimen (AI).*
- *If HBV treatment is needed and TDF cannot safely be used, the alternative recommended HBV therapy is entecavir in addition to a fully suppressive ARV regimen (BI). Other HBV treatment regimens include peginterferon alfa monotherapy or adefovir in combination with 3TC or FTC or telbivudine in addition to a fully suppressive ARV regimen (BII).*
- *Entecavir has activity against HIV; its use for HBV treatment without ART in patients with dual infection may result in the selection of the M184V mutation that confers HIV resistance to 3TC and FTC. Therefore, entecavir must be used in addition to a fully suppressive ARV regimen when used in HIV/HBV-coinfected patients (AII).*
- *Discontinuation of agents with anti-HBV activity may cause serious hepatocellular damage resulting from reactivation of HBV; patients should be advised against self-discontinuation and carefully monitored during interruptions in HBV treatment (AII).*
- *If ART needs to be modified due to HIV virologic failure and the patient has adequate HBV suppression, the ARV drugs active against HBV should be continued for HBV treatment in combination with other suitable ARV agents to achieve HIV suppression (AIII).*

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

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Approximately 5%–10% of HIV-infected persons also have chronic HBV infection, defined as testing positive for HBsAg for more than 6 months [1]. The progression of chronic HBV to cirrhosis, end-stage liver disease, and/or hepatocellular carcinoma is more rapid in HIV-infected persons than in persons with chronic HBV alone [2]. Conversely, chronic HBV does not substantially alter the progression of HIV infection and does not influence HIV suppression or CD4 cell responses following ART initiation [3-4]. However, several liver-associated complications that are ascribed to flares in HBV activity, discontinuation of dually active ARVs, or toxicity of ARVs can affect the treatment of HIV in patients with HBV coinfection [5-7]. These include the following:

- FTC, 3TC, and TDF are approved ARVs that also have antiviral activity against HBV. Discontinuation of these drugs may potentially cause serious hepatocellular damage resulting from reactivation of HBV [8].

- Entecavir has activity against HIV; its use for HBV treatment without ART in patients with dual infection may result in the selection of the M184V mutation that confers HIV resistance to 3TC and FTC. Therefore, entecavir must be used in addition to a fully suppressive ARV regimen when used in HIV/HBV-coinfected patients **(AII)** [9].

- 3TC-resistant HBV is observed in approximately 40% of patients after 2 years on 3TC for chronic HBV and in approximately 90% of patients after 4 years when 3TC is used as the only active drug for HBV in coinfected patients. Therefore, 3TC or FTC should be used in combination with other anti-HBV drugs **(AII)** [10].

- Immune reconstitution after initiation of treatment for HIV and/or HBV can be associated with elevation in transaminases, possibly because HBV is primarily an immune-mediated disease [11].

- Some ARV agents can cause increases in transaminase levels. The rate and magnitude of these increases are higher with HBV coinfection [12-13]. The etiology and consequences of these changes in liver function tests are unclear because continuation of ART may be accompanied by resolution of the changes. Nevertheless, some experts suspend

the implicated agent(s) when the serum alanine transferase (ALT) level is increased to 5–10 times the upper limit of normal. However, in HIV/HBV-coinfected persons, increases in transaminase levels can herald hepatitis B e antigen (HBeAg) seroconversion due to immune reconstitution, so the cause of the elevations should be investigated prior to the decision to discontinue medications. In persons with transaminase increases, HBeAg seroconversion should be evaluated by testing for HBeAg and anti-HBe as well as HBV DNA levels.

Recommendations for HBV/HIV-Coinfected Patients

- All patients with chronic HBV should be advised to abstain from alcohol, assessed for immunity to hepatitis A virus (HAV) infection (anti-HAV antibody total) and vaccinated if nonimmune, advised on methods to prevent HBV transmission (methods that do not differ from those to prevent HIV transmission), and evaluated for the severity of HBV infection as outlined in the *Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents* [14].

- Prior to intiation of ART, all persons who test positive for HBsAg should be tested for HBV DNA using a quantitative assay to determine the level of HBV replication **(AIII)**. Persons with chronic HBV infection already receiving ART active against HBV should undergo quantitative HBV DNA testing every 6–12 months to determine the effectiveness of therapy in suppressing HBV replication. The goal of HBV therapy with NRTIs is to prevent liver disease complications by sustained suppression of HBV replication to the lowest achievable level.

- **If not yet on therapy and HBV or HIV treatment is needed:** In persons without HIV infection, the recommended anti-HBV drugs for the treatment of persons naïve to HBV therapy are TDF and entecavir *[15-16]*. In HIV-infected patients, however, only TDF can be considered part of the ARV regimen; entecavir has weak anti-HIV activity and must not be considered part of an ARV regimen. In addition, only TDF is fully active for the treatment of persons with known or suspected 3TC-resistant HBV infection. To avoid selection of HBV-resistant variants, when possible, these agents should not be used as the only agent with anti-HBV activity in an ARV regimen **(AIII)**.

  Preferred regimen. The combination of TDF + FTC or TDF + 3TC should be used as the NRTI backbone of a fully suppressive ARV regimen and for the treatment of HBV infection *[17-19]* **(AII)**.

  Alternative regimens. If TDF cannot safely be used**,** entecavir should be used in addition to a fully suppressive ARV regimen **(AII)**; importantly, entecavir should not be considered to be a part of the ARV regimen *[20]* **(BII)**. Due to a partially overlapping HBV-resistance pathway, it is not known if the combination of entectavir + 3TC or FTC will provide additional virologic or clinical benefit compared with entecavir alone. In persons with known or suspected 3TC-resistant HBV infection, the entecavir dose should be increased from 0.5 mg/day to 1 mg/day. However, entecavir resistance may emerge rapidly in patients with 3TC-resistant HBV infection. Therefore, entecavir should be used with caution in such patients with frequent monitoring (~ every 3 months) of the HBV DNA level to detect viral breakthrough. Other HBV treatment regimens include peginterferon alfa monotherapy or adefovir in combination with 3TC or FTC or telbivudine in addition to a fully suppressive ARV regimen *[17, 21-22]*; however, data on these regimens in persons with HIV/HBV coinfection are limited **(BII)**. Due to safety concerns, peginterferon alfa should not be used in HIV/HBV-coinfected persons with cirrhosis.

- **Need to discontinue medications active against HBV:** The patient's clinical course should be monitored with frequent liver function tests. The use of adefovir dipivoxil, entecavir, or telbivudine to prevent flares, especially in patients with marginal hepatic reserve such as persons with compensated or decompensated cirrhosis, can be considered *[8]*. These alternative HBV regimens should only be used in addition to a fully suppressive ARV regimen.

- **Need to change ART because of HIV resistance:** If the patient has adequate HBV suppression, the ARV drugs active against HBV should be continued for HBV treatment in combination with other suitable ARV agents to achieve HIV suppression **(AIII)**.

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HEPATITIS C (HCV)/HIV COINFECTION (Updated December 1, 2009)

Long-term studies of patients with chronic hepatitis C virus (HCV) infection show that approximately 33% of the patients progress to cirrhosis at a median time of less than 20 years [1-2]. This rate of progression increases with older age, alcoholism, male sex, and HIV infection [3-6]. A meta-analysis demonstrated that the rate of progression to cirrhosis for persons coinfected with HCV/HIV was about three times higher than the rate for HCV mono-infected patients [5]. This accelerated rate is magnified in patients with low CD4 counts. Chronic HCV infection also complicates HIV treatment due to the increased frequency of antiretroviral (ARV)-associated hepatotoxicity [7-8]. Multiple studies have shown poor prognosis for HCV/HIV coinfection in the era of combination antiretroviral therapy (ART). It is unclear if HCV infection accelerates the rate of HIV progression [9] or if the accelerated rate primarily reflects the impact of injection drug use, which is strongly linked to HCV infection [10-11]. Although whether ART reduces the attributable morbidity/mortality from untreated HCV is unknown, the presence of chronic HCV infection influences the treatment of HIV with ARV as discussed below.

Assessment of HCV/HIV Coinfection Prior to Antiretroviral Therapy

- Prior to initiation of ART, HIV-infected patients should be screened for HCV infection with sensitive immunoassays licensed for detection of antibody to HCV in blood. To confirm the presence of chronic infection, HCV-seropositive persons should be tested for HCV RNA using a qualitative or quantitative assay [12].
- Patients with HCV/HIV coinfection should be advised to avoid alcohol consumption, use appropriate precautions to prevent transmission of both viruses to others, and receive hepatitis A (HAV) and hepatitis B (HBV) vaccines if susceptible.
- All patients with HCV/HIV coinfection should be evaluated for HCV therapy. HCV treatment is recommended according to standard guidelines with strong preference for treating patients with higher CD4 counts. For patients with lower CD4 counts (<200 cells/mm^3), it may be preferable to initiate ART and delay HCV therapy until CD4 counts increase as a result of HIV treatment [12-15].
- Concurrent treatment of both HIV and HCV is feasible but may be complicated by pill burden, drug toxicities, and drug interactions. Some notable considerations include:
    o Didanosine (ddI) should not be given with ribavirin because of the potential for drug-drug interactions leading to life-threatening ddI-associated mitochondrial toxicity including hepatomegaly/steatosis, pancreatitis, and lactic acidosis [16].
    o Zidovudine (ZDV) combined with ribavirin should be avoided when possible because the higher rates of anemia associated with the combination make ribavirin dose reduction necessary [17].
    o Abacavir (ABC) has been associated with decreased response to peginterferon plus ribavirin in some, but not all, retrospective studies; current evidence is insufficient to recommend avoiding this combination [18-20].
    o Growth factors (e.g., filgrastim and erythropoietin) may be required to manage interferon-associated neutropenia and ribavirin-associated anemia; ZDV may increase the need for adjuvant growth factors due to increased bone marrow suppression [17].

Antiretroviral Therapy in HCV/HIV Coinfection

- Hepatotoxicity: Drug-induced liver injury (DILI) following ART is more common in HIV/HCV coinfection. The greatest risk of DILI may be observed in coinfected persons with advanced liver disease (e.g., cirrhosis or end-stage liver disease) [21]. Eradication of HCV infection may decrease the likelihood of ARV-associated DILI [22].
    o Given the substantial heterogeneity in patient populations and drug regimens, comparison of DILI incidence rates for individual ARV agents across clinical trials is difficult. In such studies, the highest incidence rates of Grade 3 or 4 elevations in liver enzyme levels have been observed during therapy with ARV drugs that are no longer commonly used in clinical practice and that include stavudine (d4T) (with or without ddI), nevirapine (NVP), full-dose ritonavir (RTV) (600 mg twice daily), or tipranavir (TPV) (boosted by low-dose RTV) [23]. Also, due to the potential for concurrent fatty liver disease (steatosis), the use of d4T or ddI should be limited [24].
    o Patients should be monitored by following alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels at 1 month and then every 3 months after initiation of ART. Mild to moderate fluctuations in ALT and/or AST are typical in persons with chronic HCV infection. In the

absence of signs and/or symptoms of liver disease these fluctuations do not require interruption of ART. Significant ALT and/or AST elevation (>5 times the upper limit of the laboratory reference range) should prompt careful evaluation for signs and symptoms of liver insufficiency and for alternative causes of liver injury (e.g., acute HAV or HBV infection, hepatobiliary disease, or alcoholic hepatitis); short-term interruption of ART may be required *[25]*.

- When to start ART: The rate of liver disease (fibrosis) progression is accelerated by HIV/HCV coinfection, particularly in persons with low CD4 counts (≤350 cells/mm^3). Data derived largely from retrospective cohort studies regarding the effect of ART on the natural history of HCV disease are inconsistent *[6, 26-27]*. However, ART may slow the progression of liver disease by preserving or restoring immune function and reducing HIV-related immune activation and inflammation *[28-30]*. Thus, for most coinfected patients including those with cirrhosis, the potential benefits of ART outweigh concerns regarding DILI.
    o ART should be started in HCV/HIV-coinfected persons in accordance with the Panel's recommendation for initiating ART in ART-naïve patients.

- What to start and what not to use: Initial combination regimens for the ARV-naïve patient with HCV/HIV are the same as for persons without HCV infection. HCV infection does not significantly alter the virologic or immunologic response to effective ART *[31]*. Special considerations for ART in persons with HCV/HIV coinfection include:
    o Patients receiving or considering therapy with ribavirin should avoid ddI, d4T, and ZDV.
    o ARV agents with the greatest risk of DILI should be used with caution.
    o Cirrhotic patients should be carefully assessed for signs of liver decompensation according to the Child-Turcotte-Pugh classification system because hepatically metabolized ARV drugs may require dose modification or avoidance in patients with Child-Pugh class B and C disease. (See **Appendix B, Table 7**.)

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MYCOBACTERIUM TUBERCULOSIS DISEASE WITH HIV COINFECTION
(Updated January 10, 2011)

Panel's Recommendations:

- *The treatment of active tuberculosis (TB) disease in patients with HIV infection should follow the same principles for persons without HIV infection (AI).*

- *All HIV-infected patients with diagnosed active TB should be started on TB treatment immediately (AI).*

- *All HIV-infected patients with diagnosed active TB should be treated with antiretroviral therapy (ART) (AI).*

- *For patients with CD4 count <200 cells/mm^3, ART should be initiated within 2–4 weeks of starting TB treatment (AI).*

- *For patients with CD4 count 200–500 cells/mm^3, the Panel recommends initiation of ART within 2–4 weeks, or at least by 8 weeks after commencement of TB therapy (AIII).*

- *For patients with CD4 count >500 cells/mm^3, most Panel members also recommend starting ART within 8 weeks of TB therapy (BIII).*

- *Despite pharmacokinetic drug interactions, a rifamycin should be included in regimens for patients receiving ART, with dosage adjustment if necessary (AII).*

- *If a protease inhibitor (PI)-based regimen is used, rifabutin is the preferred rifamycin in HIV-infected patients with active TB disease due to its lower risk of substantial interactions with PIs (AII). Coadministration of rifampin and PIs (with or without ritonavir [RTV] boosting) is <u>not</u> recommended (AII).*

- *Immune reconstitution inflammatory syndrome (IRIS) may occur after initiation of ART. Both ART and TB treatment should be continued while managing IRIS (AIII).*

- *Treatment support, including directly observed therapy (DOT) of TB treatment, is strongly recommended for HIV-infected patients with active TB disease (AII).*

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

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Terminology: In this section, the terms "HIV-infected with active TB disease" and "HIV/TB disease" are used synonymously to designate HIV-infected patients with active TB disease in need of TB treatment. "HIV/TB coinfection" is not used because the term can refer to either active TB or latent TB infection (LTBI) in the presence of HIV infection and may cause confusion.

Treatment of Active TB in HIV Patients

HIV infection significantly increases the risk of progression from latent to active TB disease. The CD4 cell count influences both the frequency and severity of active TB disease *[1-2]*. Active TB also negatively affects HIV disease. It may be associated with a higher HIV viral load and more rapid progression of HIV disease *[2-3]*.

Active pulmonary or extrapulmonary TB disease requires prompt initiation of TB treatment. The treatment of active TB disease in HIV-infected patients should follow the general principles for persons without HIV (**AI**). Treatment of drug-susceptible TB disease should include a standard regimen that consists of isoniazid (INH) + a rifamycin (rifampin or rifabutin) + pyrazinamide + ethambutol given for 2 months, followed by INH + a rifamycin for 4 to 7 months *[4]*. A more complete discussion of the diagnosis and treatment of TB disease and LTBI in HIV patients is available in the ***Guidelines for Preventing and Treating Opportunistic Infections in HIV-Infected Adults and Adolescents*** *[4]*.

All patients with HIV/TB disease should be treated with ART **(AI)**. Important issues related to the use of ART in patients with active TB disease include: (1) when to start ART, (2) significant pharmacokinetic drug interactions with rifamycins, (3) the additive toxicities associated with ARV and TB drugs, (4) the development of IRIS with TB after

ART initiation, and (5) the need for treatment support including DOT and the integration of HIV and TB care and treatment.

When to Start Antiretroviral Therapy

Patients Diagnosed with TB While Receiving ART

At the time TB treatment is initiated in patients receiving ART, the patient's ARV regimen should be assessed with particular attention to potential pharmacokinetic interactions with rifamycins (discussed below). The patient's regimen may need to be modified to permit use of the optimal TB treatment regimen.

Patients Receiving Treatment for Active TB but Not Yet on ART

When to initiate ART in patients with active TB has been the subject of differing recommendations based upon observational studies and expert opinion *[4-6]*. Two randomized controlled trials now provide some additional evidence regarding this issue. In these studies, concomitant administration of therapy for both TB disease and HIV infection resulted in significant reduction in HIV/TB disease mortality *[7-8]*. The results of an ACTG trial will soon be available and may provide further guidance or support for recommendations concerning when to start ART in patients with active TB.

In the SAPIT study from South Africa, HIV-infected patients with smear-positive TB and CD4 counts <500 cells/mm^3 were randomized to one of three treatment arms: integrated therapy with ART initiated either during the first 4 weeks of TB therapy or after the second month (i.e., during the continuation phase of TB therapy) or sequential therapy with ART initiated after the conclusion of standard TB therapy. The sequential arm was stopped when an early analysis demonstrated a 55% reduction in mortality in the combined two integrated arms compared with the sequential therapy arm *[7]*. In the CAMELIA study from Cambodia *[8]*, patients with CD4 counts <200 cells/mm^3 were randomized to initiate ART at 2 weeks or at 8 weeks of TB treatment. A 34% reduction in mortality was seen with ART initiation at 2 weeks compared with initiation at 8 weeks (p = 0.002). The populations in these two studies differed: the median CD4 count among SAPIT participants was 140–150 cells/mm^3; in the CAMELIA trial, the median CD4 count at entry was 25 cells/mm^3. Low CD4 count at study baseline predicted poorer survival in both studies. Both studies demonstrated excellent ART response: 90% and >95% of participants achieved suppressed HIV RNA (<400 copies/mL) at 12 months in the SAPIT study and CAMELIA trial, respectively. Although in both studies IRIS was more common in patients initiating ART earlier, the syndrome was not associated with mortality.

Based on the available data and the potential benefits of ART in patients with active TB, the Panel recommends the following:
- *For patients with CD4 count <200 cells/mm^3, ART should be initiated within 2–4 weeks of starting TB treatment (AI).*
- *For patients with CD4 count 200–500 cells/mm^3, the Panel recommends initiation of ART within 2–4 weeks, or at least by 8 weeks after commencement of TB therapy (AIII).*
- *For patients with CD4 count >500 cells/mm^3, most Panel members also recommend starting ART within 8 weeks of TB therapy (BIII).*

ART should be started as early as feasible for all HIV-infected pregnant women with active TB, both for maternal health and for prevention of mother-to-child transmission (PMTCT) of HIV **(AIII)**. An augmented immune or inflammatory response in patients with some manifestations of TB, such as meningitis, pericarditis, or respiratory failure, might be life threatening. In these circumstances, delaying initiation of ART briefly beyond recommended intervals may be appropriate **(CIII)**.

Drug Interaction Considerations

A rifamycin is a crucial component for the treatment of drug-sensitive TB. However, both rifampin and rifabutin are inducers of the hepatic cytochrome P (CYP) 450 and uridine diphosphate gluconyltransferase (UGT) 1A1 enzymes and are associated with interactions with most ARV agents including all PIs, non-nucleoside reverse transcriptase

inhibitors (NNRTIs), maraviroc (MVC), and raltegravir (RAL). Rifampin is a strong enzyme inducer, leading to enhanced drug clearance and greater reduction in ARV drug exposure. Rifabutin, a weaker enzyme inducer, is an alternative to rifampin. Because rifabutin is a substrate of the CYP 450 enzyme system, its metabolism may be affected by the NNRTI or PI as discussed below. **Tables 15a and 15b** outline the magnitude of these interactions and provide dosing recommendations when rifamycins and selected ARV drugs are used concomitantly. After determining the drugs and doses to use, patients should be closely monitored to assure good control of both TB and HIV. Suboptimal HIV suppression or suboptimal response to TB treatment should prompt assessment of drug adherence, subtherapeutic drug levels (consider therapeutic drug monitoring [TDM]), and acquired drug resistance.

Rifamycins and NNRTIs

Rifampin induces metabolism of both nevirapine (NVP) *[9]* and efavirenz (EFV) *[10]* leading to reduced NNRTI drug exposure. The extent of induction is less pronounced with EFV than with NVP. Despite the interactions, some observational studies suggest that good virologic, immunologic, and clinical outcomes may be achieved with standard doses of either EFV *[11-12]* or NVP *[13-14]* when combined with rifampin.

Rifabutin does not significantly affect EFV and NVP drug exposure. Because both EFV and NVP can induce rifabutin metabolism, an increased rifabutin dose is recommended. Few data exist on the use of rifampin and etravirine (ETR); however, because rifampin is expected to induce ETR metabolism, concomitant use is not recommended. Rifabutin is recommended in this situation.

Rifamycins and PIs

Rifampin can significantly decrease PI drug exposure, despite ritonavir (RTV) boosting, with resultant risk of ART failure *[15-16]*. Some investigators had explored the use of an additional RTV dose or doubling PI doses in attempt to overcome rifampin's induction effect. However, a high rate of serious hepatotoxicity and significant gastrointestinal intolerance resulted in terminations of these studies *[15, 17-18]*. Therefore, coadministration of rifampin and PIs is **not recommended** (**AII**).

Because rifabutin has a less significant impact on the pharmacokinetics of RTV-boosted PIs, it is the preferred rifamycin to use with PI-based regimens **(AII)**. Both RTV-boosted and -unboosted PIs can inhibit rifabutin metabolism and the optimal dose of rifabutin is yet to be defined. Most PI manufacturers suggest rifabutin 150 mg every other day (instead of normal doses of 300 mg once daily). Lower than expected drug exposure *[19-20]* and acquired rifamycin resistance have been reported in HIV-infected patients who received PI-based regimens and intermittent doses of rifabutin *[19, 21]*. If available, TDM can be helpful in assessing the adequacy of rifabutin drug exposure.

Rifamycins and MVC or RAL

MVC is a substrate of CYP3A4 and rifampin can significantly reduce MVC concentration. If concomitant use is necessary, the MVC dose should be increased. Rifabutin may be an alternative rifamycin. (See **Table 15d** for recommended doses of MVC used with rifamycins.)

Rifampin, a strong UGT1A1 enzyme inducer, significantly accelerates the metabolism of RAL *[22]*. When used in combination with rifampin, the RAL dose should be increased to 800 mg twice daily. Rifabutin has minimal effect on RAL metabolism and may be more appropriate in this situation.

Anti-TB/ARV Toxicities

ARV agents and TB drugs, particularly INH, rifamycin, and pyrazinamide, can cause drug-induced hepatitis. These first-line TB drugs should still be used for treatment of active TB disease, even with coadministration of other potentially hepatotoxic drugs or in the presence of baseline liver disease **(AIII)**. Patients receiving drugs with potential hepatotoxicity should have frequent monitoring for clinical symptoms and signs of hepatitis and laboratory monitoring for hepatotoxicity. Peripheral neuropathy can occur with INH, didanosine (ddI), or stavudine (d4T) or may be a manifestation of HIV. All patients receiving INH should also receive supplemental pyridoxine to reduce peripheral

neuropathy. Patients should be monitored closely for signs of drug-related toxicities and receive alternatives to ddI or d4T.

IRIS with TB and ARV Agents

IRIS occurs in two forms, "unmasking" and "paradoxical." The mechanism is the same for both forms of IRIS: restoration of immune competence by administration of ARV agents, resulting in an exuberant host response to TB bacilli and/or antigens. Unmasking IRIS refers to the initial clinical expression of active TB occurring soon after ARV agents are started. Paradoxical IRIS refers to the worsening of TB clinical manifestations after ARV agents are started in patients who are receiving TB treatment. Severity of IRIS ranges from mild to severe to life threatening. IRIS has been reported in 8% to greater than 40% of patients starting ART after TB is diagnosed, although the incidence depends on the definition of IRIS and the intensity of monitoring *[23-24]*.

Predictors of IRIS include CD4 count <50 cells/mm^3, higher on-ART CD4 counts, high pre-ART and lower on-ART HIV viral loads, severity of TB disease, especially high pathogen burden, and less than 30-day interval between initiation of TB and HIV treatments. *[5, 25-29]*. Most IRIS in HIV/TB disease occurs within 3 months of the start of TB treatment. Delaying the start of ART for 2–8 weeks may reduce the incidence and severity of IRIS but must be weighed against the potential benefit of earlier ART in improving immune function and preventing progression of HIV disease and mortality.

Milder or moderately severe cases of IRIS can be managed symptomatically or treated with nonsteroidal inflammatory agents. More severe cases can be successfully treated with corticosteroids. A recent randomized, placebo-controlled trial demonstrated benefit of corticosteroid treatment as measured by decreasing days of hospitalization and Karnofsky performance score without adverse consequences *[30]*. In the presence of IRIS, neither TB therapy nor ART should be stopped because both therapies are necessary for the long-term health of the patient **(AIII)**.

Immune Reconstitution with ART: Conversion to Positive Tuberculin Skin Test (TST) and Interferon-Gamma (IFN-γ) Release Assay (IGRA)

Immune reconstitution with ART may result in unmasking LTBI (i.e., conversion of a previously negative TST to a positive TST or a positive IGRA for *Mycobacterium tuberculosis*-specific proteins). A positive IGRA, similar to a positive TST, is indicative of LTBI in the absence of evidence of active TB disease *[31]*. Because treatment for LTBI is indicated in the absence of evidence of active TB disease, clinicians should be aware of this phenomenon. Patients with a negative TST or IGRA and advanced HIV disease (i.e., CD4 count <200 cells/mm^3) should have a repeat TST or IGRA after initiation of ART and CD4 count increase to >200 cells/mm^3 *[32]* **(BII)**.

Caring for Patients with HIV and TB

Integration of diagnosis and treatment and/or close collaboration between TB and HIV clinicians, health care institutions, and public health programs are necessary in order to improve medication adherence and TB treatment completion rates, reduce toxicities, and maximize HIV outcomes in HIV-infected patients with active TB disease *[4]*. These patients should receive treatment support, including adherence counseling and DOT, corresponding to their needs **(AII)**. ART simplification or use of coformulated fixed-dose combinations may also be helpful to improve drug adherence.

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